

Population Pharmacokinetics of Intranasal Scopolamine

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Introduction: An intranasal gel dosage formulation of scopolamine (INSCOP) was developed for the treatment of Space Motion Sickness (SMS). The bioavailability and pharmacokinetics (PK) was evaluated using data collected in Phase II IND protocols. We reported earlier statistically significant gender differences in PK parameters of INSCOP at a dose level of 0.4 mg. To identify covariates that influence PK parameters of INSCOP, we examined population covariates of INSCOP PK model for 0.4 mg dose.

Methods: Plasma scopolamine concentrations versus time data were collected from 20 normal healthy human subjects (11 male/9 female) after a 0.4 mg dose. Phoenix NLME was employed for PK analysis of these data using gender, body weight and age as covariates for model selection. Model selection was based on a likelihood ratio test on the difference of criteria (-2LL). Statistical significance for base model building and individual covariate analysis was set at $P < 0.05$ (Δ (-2LL) = 3.84).

Results: A one-compartment pharmacokinetic model with first-order elimination best described INSCOP concentration-time profiles. Inclusion of gender, body weight and age as covariates individually significantly reduced -2LL by the cut-off value of 3.84 ($P < 0.05$) when tested against the base model. After the forward stepwise selection and backward elimination steps, gender was selected to add to the final model which had significant influence on absorption rate constant (k_a) and the volume of distribution (V) of INSCOP. The final model structure was list below:

$$\begin{aligned}K_a &= \text{tv}K_a * \exp(\text{dKadSEX1} * (\text{SEX} == 1)) * \exp(\text{nK}_a) \\V &= \text{tv}V * \exp(\text{dVdSEX1} * (\text{SEX} == 1)) * \exp(\text{nV}) \\Cl &= \text{tv}Cl * \exp(\text{nCl})\end{aligned}$$

The population pharmacokinetic parameter estimates derived from base and the final model were shown in Table 1

Parameter (Mean±SE)	Units	Base Model	Covariate Model
<u>tvKa</u>	1/h	2.89±0.41	1.11±0.06
<u>tvV</u>	L	2129.93±162.8	1244.21±35.54
<u>tvCl</u>	L/h	343.83±32.60	466.4±27.24
Criteria(-2LL)		2785.5	2410.9
N	20		

Table 1

Conclusion: A population pharmacokinetic model for INSCOP has been identified and gender was a significant contributing covariate for the final model. The volume of distribution and Ka were significantly higher in males than in females which confirm gender-dependent pharmacokinetics of scopolamine after administration of a 0.4 mg dose.